

68693

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Ganapathy Krishnan Examiner #: 79271 Date: 6/12/02
Art Unit: 1623 Phone Number 305-4837 Serial Number: C9909797
Mail Box and Bldg/Room Location: 8D08 Results Format Preferred (circle): PAPER DISK E-MAIL
8B19

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: compositions of polysaccharides derived from heparin, their preparation and pharmaceutical compositions

Inventors (please provide full names): Jacques Diaz, Christelle Pecquet, Elisabeth Perrin, Christian Viskou.

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Search claims 1-46.

For claims 18, 19, 20 need structure search.

Point of Contact:
Susan Hanley
Technical Info. Specialist
CM1 6B05 Tel: 305-4053

BEST AVAILABLE COPY

RECEIVED
JUN 13 2002
STIC

Vendors and cost where applicable

WHAT IS CLAIMED IS:

1. A composition comprising at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin, said at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin having a mean molecular weight in the range from 1500 to 3000 daltons; an anti-Xa activity in the range from 94 to 150 IU/mg; an anti-IIa activity in the range up to 10 IU/mg; and an anti-Xa activity:anti-IIa activity ratio greater than 10:1.

2. A composition comprising at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin in which the alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at least one end.

3. A composition according to claim 1 in which the alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at at least one end.

4. A composition according to claim 2 having anti-Xa activity in the range of 125 to 150 IU/mg.

5. A composition according to claim 2 having a mean molecular weight in the range of 2000 to 3000 daltons.

6. A composition according to claim 2 having anti-Xa activity in the range of 140 to 150 IU/mg and a mean molecular weight in the range of 2000 to 3000 daltons.

7. A composition according to claim 2, in which the at least one alkali or alkaline-earth metal salt is a sodium, potassium, calcium or magnesium salt.

8. A composition according to claim 2, having an anti-IIa activity in the range of up to 5 IU/mg.

9. A composition according to claim 2, having an anti-Xa activity:anti-IIa activity ratio greater than 25.

10. The method of preparing at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin comprising:

depolymerizing a quaternary ammonium salt of the benzyl ester of heparin in an organic medium with a base with a pKa greater than 20;

converting the quaternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt;

saponifying the ester; and

optionally purifying the product.

11. The method according to claim 10, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has a mean molecular weight in the range of 1500 to 3000 daltons.

12. The method according to claim 10, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has an anti-Xa activity in the range of 94 to 150 IU/mg.

13. The method according to claim 10, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has an anti-IIa activity in the range of up to 10 IU/mg.

14. The method according to claim 10, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has an anti-Xa activity:anti-IIa activity ratio greater than 10:1.

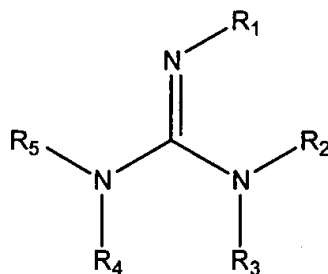
15. The method according to claim 10, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin comprises 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at at least one end.

16. The method according to claim 10, in which the quaternary ammonium salt of the benzyl ester of heparin is a benzethonium, cetylpyridinium, or cetyltrimethylammonium salt.

17. The method according to claim 10, in which the base with a pKa greater than 20 is chosen from 1,5,7-triazabicyclo-[4.4.0]-dec-5-ene, 2-tert-

butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine, a base of guanidine, and a base of phosphazene.

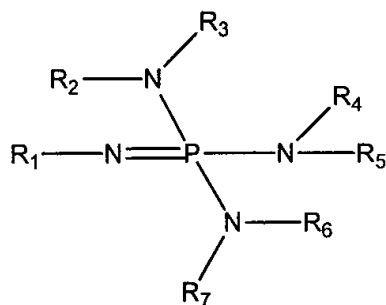
18. The method according to claim 17, in which the base of guanidine comprises:



where R₁ is hydrogen or alkyl, and where R₂, R₃, R₄, and R₅, which are identical or different, and each is a C₁-C₆ alkyl.

19. The method according to claim 18, where R₁ is hydrogen, and R₂, R₃, R₄, and R₅ are each methyl.

20. The method according to claim 17, in which the base of phosphazene comprises:



where R_1 to R_7 are identical or different, and each is a C_1 - C_6 alkyl.

21. The method according to claim 10, in which the mol ratio of the base with a pK_a greater than 20 to the quaternary ammonium salt of the benzyl ester of heparin ranges from 0.2:1 to 5:1.

22. The method according to claim 10, in which the degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin ranges from 50 to 100%.

23. The method according to claim 10, in which the quaternary ammonium salt of the benzyl ester of depolymerized heparin is converted to a sodium salt by treating the reaction medium with an alcoholic solution of sodium acetate.

24. The method according to claim 10, in which the saponification is carried out by an alkali metal hydroxide.

25. The method according to claim 10, in which the purification is carried out by hydrogen peroxide.

26. The method of preparing at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin comprising:

depolymerizing a quaternary ammonium salt of the benzyl ester of heparin in an organic medium with sodium imidazolate;

converting the quaternary ammonium salt of the benzyl ester of the depolymerized heparin to a sodium salt;

saponifying the ester; and

optionally purifying the product.

27. The method according to claim 26, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has a mean molecular weight in the range from 1500 to 3000 daltons.

28. The method according to ~~claim~~ 26, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has an anti-Xa activity in the range from 94 to 150 IU/mg.

29. The method according to ~~claim~~ 26, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has an anti-IIa activity in the range of up to 10 IU/mg.

30. The method according to ~~claim~~ 26, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin has an anti-Xa activity:anti-IIa activity ratio greater than 10:1.

31. The method according to ~~claim~~ 26, in which the at least one alkali or alkaline-earth metal salt of at least one sulphated polysaccharide of heparin comprises 2 to 26 saccharide units and has a 4,5-unsaturated glucuronic acid 2-O-sulphate unit at at least one end.

32. The method according to ~~claim~~ 26, in which the quaternary ammonium salt of the benzyl ester of heparin is a benzethonium, cetylpyridinium, or cetyltrimethylammonium salt.

33. The method according to ~~claim~~ 26, in which the mol ratio of the sodium imidazolate to the quaternary ammonium salt of the benzyl ester of heparin ranges from 0.2:1 to 5:1.

34. The method according to ~~claim~~ 26, in which the degree of esterification of the quaternary ammonium salt of the benzyl ester of heparin ranges from 50 to 100%.

35. The method according to ~~claim~~ 26, in which the quaternary ammonium salt of the benzyl ester of depolymerized heparin is converted to a sodium salt by treating the reaction medium with an alcoholic solution of sodium acetate.

36. The method according to ~~claim~~ 26, in which the saponification is carried out by an alkali metal hydroxide.

37. The method according to claim 26, in which the purification is carried out by hydrogen peroxide.

38. A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 2, in an amount efficacious for the treatment of venous thrombosis.

39. A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition prepared according to the method as claimed in claim 10, in an amount efficacious for the treatment of venous thrombosis.

40. A method of treating venous thrombosis in a patient in need of such treatment, comprising administering to the patient a composition prepared according to the method as claimed in claim 26, in an amount efficacious for the treatment of venous thrombosis.

41. A method of treating arterial thrombotic accidents in a patient in need of such treatment, comprising administering to the patient a composition as claimed in claim 2, in an amount efficacious for the treatment of arterial thrombotic accidents.

42. A method of treating arterial thrombotic accidents in a patient in need of such treatment, comprising administering to the patient a composition prepared according to the method as claimed in claim 10, in an amount efficacious for the treatment of arterial thrombotic accidents.

43. A method of treating arterial thrombotic accidents in a patient in need of such treatment, comprising administering to the patient a composition prepared according to the method as claimed in claim 26, in an amount efficacious for the treatment of arterial thrombotic accidents.

44. A method of treating a patient comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition according to claim 2 is an active ingredient present in an amount efficacious for such treatment.

45. A method of treating a patient comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition produced by the method according to claim 10 is an active ingredient present in an amount efficacious for such treatment.

46. A method of treating a patient comprising the administration of a solution of a pharmaceutical composition by the subcutaneous, intramuscular, intravenous, or pulmonary route, in which a composition produced by the method according to claim 26 is an active ingredient present in an amount efficacious for such treatment.